Remarks

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

As a preliminary matter, Applicants wish to thank the Examiner for her helpful discussion with Applicants' representative in the interview of July 26, 2002. During the interview, the differences between the presently claimed invention and the cited art were discussed.

I. Support for Amendments

Support for new claim 57 may be found through out the specification, *inter alia*, at page 9 lines 20-28, page 13 line 20 to page 15 line 22, and in Example 1.

Support for new claim 58 may be found through out the specification, *inter alia*, at page 8 lines 17-20, page 9 lines 25-28, and in Example 1.

Support for new claim 59 may be found through out the specification, *inter alia*, at page 12 lines 23-25, and in Example 1.

Support for new claim 60 may be found through out the specification, *inter alia*, at page 6 lines 9-25, and in Example 1.

Support for new claim 61 may be found through out the specification, *inter alia*, at page 6 lines 9-25, page 20 line 24 to page 21 line 14, and in Example 1.

Support for new claim 62 may be found through out the specification, *inter alia*, at page 6 lines 9-25, page 20 lines 14-23, and in Example 1.

Support for new claim 63 may be found through out the specification, *inter alia*, at page 6 lines 9 to page 7, and in Example 1.

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II. Status of the Claims

Upon entry of the foregoing amendment, claims 1, 2, 6, 12, 16-20, 22, 25, 28, 29, 31, 32, and 54-63 are pending in the application, with claims 1 and 57 being the independent claims.

III. Summary of the Office Action

In the Office Action dated October 3, 2001, the Examiner maintained two rejections of pending claims 1, 2, 6, 12, 16-20, 22, 25, 28, 29, 31, and 32 and extended the rejections to claims 54-56. Applicants respectfully offer the following remarks to overcome these rejections.

IV. The Rejection of Claims 1, 2, 6, 12, 16-20, 22, 25, 28, 29, 31, 32, and 54-57 Under 35 U.S.C. § 102(e) as Anticipated By Burmer Must Be Withdrawn

In the Office Action at pages 2-3, section 2, the Examiner maintained the rejection of claims 1, 2, 6, 12, 16-20, 22, 25, 28, 29, 31, and 32, and rejected claims 54-56, under 35 U.S.C. § 102(e), alleging that the claims are anticipated by Burmer, U.S. Patent No. 5,726,022 (hereinafter "Burmer"). Applicants respectfully request reconsideration and withdrawal of this rejection.

Claim 1 is drawn to a method for making a nucleic acid molecule by mixing one or more nucleic acid templates with (i) one or more polypeptides having polymerase activity and/or reverse transcriptase activity and (ii) a primer-adapter nucleic acid molecule, to form a mixture and incubating said mixture under conditions sufficient to make a first nucleic acid molecule complementary to all or a portion of said template and comprising said primer-adapter nucleic acid molecule, wherein said primer-adapter nucleic acid molecule comprises

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one or more ligands and one or more cleavage sites and one or more of said templates is an RNA molecule. Claims 2, 6, 12, 16-20, 22, 25, 28, 29, 31, 32, and 54-56 depend—directly or indirectly—from claim 1. Newly presented claim 57 is drawn to a method for making one or more nucleic acid molecules by mixing one or more mRNA molecules with (i) one or more polypeptides having reverse transcriptase activity and (ii) at least one primer-adapter nucleic acid molecule, to form a mixture and incubating said mixture under conditions sufficient to make one or more first nucleic acid molecules complementary to all or a portion of said one or more mRNA molecules, wherein said one or more first nucleic acid molecules comprise at least one primer-adapter nucleic acid molecule and wherein said at least one primer-adapter nucleic acid molecule comprises one or more ligands and one or more cleavage sites. Claims 58-63 depend from claim 57. Claim 1 requires that one or more of said templates is an RNA molecule and claim 57 requires the use of one or more mRNA molecules, thus, all the pending claims require mixing one or more RNA template nucleic acid molecules with the recited polypeptides and a primer-adapter nucleic acid molecule.

A reference anticipates a claim "only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. V. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987) Burmer does not teach mixing an RNA template molecule with a polypeptide having polymerase and/or reverse transcriptase activity *and* a primer-adapter nucleic acid molecule and, therefore, does not anticipate the present invention.

In support of this rejection as applied to claims 1, 2, 12, 16, 17, 25, 28, and 29, the Examiner alleges:

> Burmer discloses that an adapter with a restriction site is ligated to a first nucleic acid sample and optionally the adapter may contain a ligand binding end. Further, Brumer discloses that if the first and second nucleic acid fragment are amplified, they are amplified with primers containing a ligand

> binding end and a sequence complementary to the adapters (See column 2, lines 39-48). The teachings are inherent that the primer of Brumer contains all the limitation[s] as recited in claims 1, 2, 12, 16-17, 25, 28, 29." (Office Action, page 2)

Applicants respectfully disagree with the Examiner's conclusion. In the section immediately preceding that to which the Examiner points (column 2 lines 29-38), Burmer indicates that the nucleic acids are fragmented by restriction endonuclease digestion and that the nucleic acid samples are preferably cDNA samples derived from RNA. Thus, Burmer prepares cDNA from RNA and then digests the cDNA to produce fragments. The fragments are then ligated to the adapters to which the Examiner points. At no point does Burmer teach mixing an RNA template with an primer-adapter as presently called for in the claims.

In rejecting the remaining claims, the Examiner asserts:

> Burmer discloses that amplification may be done by PCR, LCR or TAS (see column 8, lines 47-52) (as recited in claims 12, 16). This indicates that the polypeptides as listed in claim 6 are involved in the method of the invention, for example, reverse transcriptase and *Taq* DNA polymerase. The isolation step is done by first removing the adaptors by restriction enzyme, capturing the nucleic acid containing the ligand and then the nucleic acid that were not captured is isolated (see column 2, lines 56-59) (as recited in claims 20 and 31-32). The ligand includes hapten (see column 7, line 4) (as recited in claims 18-9). The solid support is described in column 7, lines 37-48 (as recited in claims [sic] 22). (Office Action, pages 2-3).

The Examiner further asserts that newly added claims 54-56 are anticipated by Burmer "since Burmer disclose[s] that nucleic acid samples are cDNA derived from RNA (See column 2, lines 34-35)."

Applicants respectfully submit that none of the portions of Burmer to which the Examiner points teach mixing an RNA template with a primer-adapter as presently called for in the claims. Since Burmer does not disclose all of the elements of the presently claimed invention, Burmer does not anticipate the present claims. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

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V. The Rejection of Claims 1, 2, 6, 12, 16, 17-19, 25, 28, 29, and 31 Under 35 U.S.C. § 103(a) as Obvious Over Frohman in View of Lohman, et al. Must Be Withdrawn

In the Office Action at pages 3-4, section 3, the Examiner maintained the rejection of claims 1, 2, 6, 12, 16, 17-19, 25, 28-29, and 31, and rejected claims 54-56, under 35 U.S.C. § 103(a), alleging that the claimed invention is obvious over the teachings of Frohman (PCR Protocols, 1990, pp. 28-38, hereinafter "Frohman") in view of Lohman, *et al.* U.S. Patent No. 5,631,147 (hereinafter "Lohman"). Applicants respectfully request reconsideration and withdrawal of this rejection.

Claim 1 is drawn to a method for making a nucleic acid molecule by mixing one or more nucleic acid templates with (i) one or more polypeptides having polymerase activity and/or reverse transcriptase activity and (ii) a primer-adapter nucleic acid molecule, to form a mixture and incubating said mixture under conditions sufficient to make a first nucleic acid molecule complementary to all or a portion of said template and comprising said primer-adapter nucleic acid molecule, wherein said primer-adapter nucleic acid molecule comprises one or more ligands and one or more cleavage sites and one or more of said templates is an RNA molecule. Claims 2, 6, 12, 16-19, 25, 28, 29, 31, and 54-56 depend—directly or indirectly—from claim 1. Newly presented claim 57 is drawn to a method for making one or more nucleic acid molecules by mixing one or more mRNA molecules with (i) one or more polypeptides having reverse transcriptase activity and (ii) at least one primer-adapter nucleic acid molecule, to form a mixture and incubating said mixture under conditions sufficient to make one or more first nucleic acid molecules complementary to all or a portion of said one or more mRNA molecules, wherein said one or more first nucleic acid molecules comprise at least one primer-adapter nucleic acid molecule and wherein said at least one primer-adapter

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nucleic acid molecule comprises one or more ligands and one or more cleavage sites. Claims 58-63 depend from claim 57. Thus, all the pending claims require mixing one or more RNA template nucleic acid molecules with the recited polypeptides and a primer-adapter nucleic acid molecule.

MPEP 2143.01 reads in pertinent part:

> If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion to make the proposed modification.

When this rejection was first advanced, the Examiner characterized the disclosure of Frohman as teaching a method that "involves a[n] adapter primer containing restriction sites." (Office Action of October 3, 2001, page 4). After acknowledging that Frohman did not teach that the adapter primers comprise the ligands required by claim 1, the Examiner attempted to remedy the deficiencies of Frohman by combining the teachings of Frohman with those of Lohman. The Examiner went on to assert:

> One of ordinary skill in the art would have been motivated to combine the teachings of Frohman and Lohman et al. to make instant invention with a reasonable expectation of success because in order to label the adapter primer of Frohman, the method of Lohman et al. involves using the primer attached to ligand and such that the movement of the amplification of the method of Frohman is tracked. Thus it would have been prima facie obvious to carry out the method as claimed.

Office Action of October 3, 2001, pages 4 and 5, section 4.

In maintaining this rejection in the present Action, the Examiner asserts "the motivation is that the method of Lohman, *et al.* involves using the primer attached to ligand and such that the movement of the amplification of the method of Frohman is tracked (This means that the amplification products are detected.)"

Applicants respectfully submit that the Examiner has improperly combined two references to reach the claimed invention. The two references can not be combined because

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the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose.

The purpose of the Frohman reference is the cloning of full length cDNA molecules. In order to clone the amplified fragments in a controlled orientation, the amplified fragments produced with the restriction-site-containing primers of Frohman are digested with restriction endonucleases to permit directional cloning of the amplified fragments (see page 32). Thus, the purpose of the restriction sites in the primers of Frohman is to produce an amplified product containing restrictions sites that *can be cleaved* in both strands to produce the customary "sticky ends" for subsequent ligation.

In contrast to the cloning methods of Frohman, the purpose of the methods disclosed in the Lohman reference is the *in situ* amplification of target nucleic acid sequences (column 3, line 58). In order to accomplish this, the reaction requires that a nick be introduced in the amplified product. The nicking activity "is of great importance, as it is nicking which perpetuates the reaction and allows subsequent rounds of target amplification to initiate" (column 7, lines 54-56). This nick is introduced by cleaving only one strand of the amplified product using a thermostable endonuclease. The amplification product is prepared by incorporating modified nucleotides into either the primer or the amplification reaction to produce one strand of the amplified product that is resistant to cleavage. (Column 7, lines 59 et seq.) Thus, in order to carry out the intended purpose of the methods disclosed in the Lohman patent, the product of the amplification reaction must be a nucleic acid molecule that *cannot be cleaved* but instead can be partially cut to produce the required single strand nick.

Clearly, the methods of the two references provide completely different products in the amplification reactions. Further, the products used in the two processes are mutually exclusive; the cleavable product of the Frohman method will not work in the Lohman method

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and non-cleavable product of the Lohman reaction will not work in the Frohman method. Thus, any combination of the methods of the cited references would result in the methods being rendered unfit for their intended purposes.

Applicants respectfully submit that there is no motivation to combine the cited references and request reconsideration and withdrawal of this rejection

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

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Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Version with markings to show changes made

New claims 57-63 have been added.